COST D32 Action
Chemistry under High-Energy Microenvironments
Final Meeting Krakow (Poland,) March 29-April1 2009

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EXPLORING MULTICOMPONENT AND HETEROCYCLIC COUPLING REACTIONS USING MICROREACTOR TECHNOLOGY

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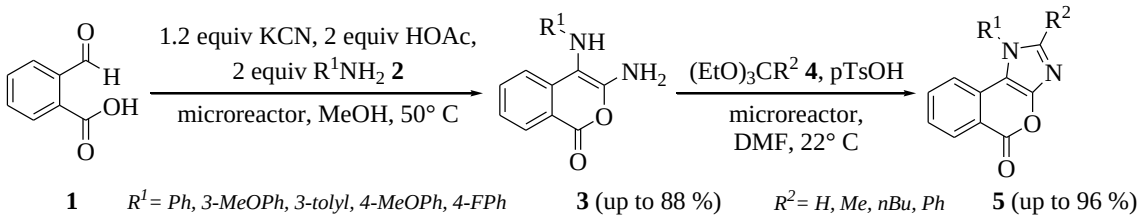
Keywords: microreactor technology, efficient scalability, multicomponent reactions, transition metal-catalyzed reactions

During the last decades, microreactor technology has gained an enormous interest in both academic research and within the pharmaceutical industry. Extensive research is performed to develop new types of microreactors, and some applications have been investigated thoroughly. An advantage of this technology arises from (some) acceleration of reactions. Owing to the structure of the reactor (with capillaries in the range of 100 μm), the mixing rate is extremely high and the temperature profile is very narrow due to an increased surface-to-volume ratio, compared to those in batch vessels. Back-mixing is minimized and the reaction time is narrowly controlled. As a consequence, switching from batch to continuous processing is beneficial because of the use of similar conditions, minimizing the expensive and time-consuming process of scaling-up.

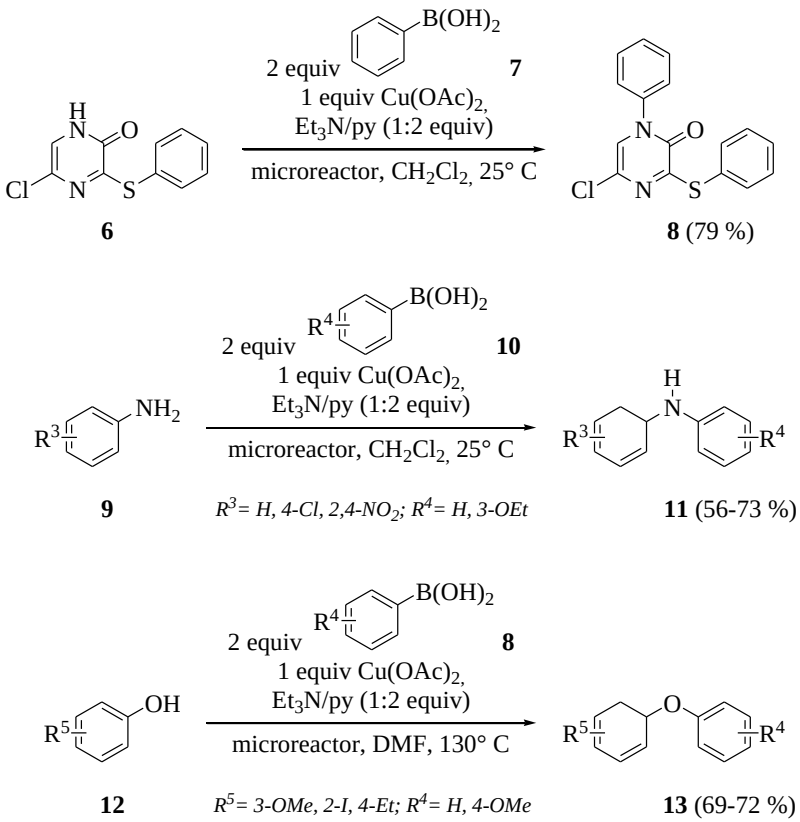
Our group has been active in optimizing multicomponent reactions under microreactor conditions and in evaluating the limits of the use of microreactor technology. We have shown that it is possible to prepare a library of compounds in a very fast way. It is quite easy to prepare bigger amounts of products which is extremely valuable in the pharmaceutical industry if a few kilograms of product need to be prepared for testing.

Following our research about the formation of 3,4-diamino-1*H*-isochromen-1-ones under microreactor conditions (the first study in which hydrogen cyanide is produced and reacted further in a microreactor system),[1] a ring closure of the vicinal amino groups was evaluated in order to attach an imidazole core to the molecule (Scheme 1).[2] Imidazoles are currently important in view of their potential to form ionic liquids after quaternisation of the nitrogen atom.



Scheme. 1. Continuous synthesis of 1*H*-isochromeno[3,4-*d*]imidazol-5-ones in two microreactor steps.

Further, we have elaborated a continuous flow procedure for the copper(II)-mediated *N*- and *O*-arylation of various compounds with arylboronic acids (Scheme 2).[3] Despite the large interest in copper-mediated heteroatom arylation during the last years, to our knowledge no earlier studies were performed on the use of microreactors for this purpose. Using our protocol, the coupling products could be continuously generated in good yields, paving the way for efficient scalability.



Scheme. 2. Copper(II)-mediated *N*- and *O*-arylations of pirazinone **6**, anilines **9** and phenols **12** with arylboronic acids using a commercial microreactor setup.

References
[1] Davy R. J. Acke and Christian V. Stevens, *Green Chem.*, **2007**, *9*, 386-390.
[2] Davy R. J. Acke, Christian V. Stevens and Bart I. Roman, *Org. Process Res. Dev.*, **2008**, *12* (5), 921-928.
[3] Brajendra K. Singh, Christian V. Stevens, Davy R. J. Acke, Virinder S. Parmar and Erik V. Van der Eycken, *Tetrahedron Lett.*, **2009**, *50*, 15-18.